DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/24/2010 has been entered.

2. Applicant's amendment of claim 1 in the paper filed on 10/29/2010 is acknowledged.

Claims 1, 5-10, 16, 19, and 20 are pending and at issue.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 103(a)

3. The rejection of under 35 USC § 103(a) is withdrawn. Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

Rejections that are Maintained

Claim Rejections Maintained - 35 USC § 112, Second Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 5-10, 16, 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 1 recites a primer for "elongating the A-strand" which primer has a sequential base sequence which is found in the A-strand. In other words, The A-strand primer has a sequence identical to a sequence of the A-strand which is used for elongating the A-strand. It is unclear how this can be done as the shared sequences are identical and not complementary and it is unknown, not recited, and not disclosed in the specification as to how the A-strand primer will bind to the A-strand in order to initiate elongation.

7. The relationship in claim 1 of "a" partial A-strand region in the B-strand primer and "a" complementary partial A-strand sequence in the B-Strand is unclear and hence indefinite. There is no clear language indicating that the partial A-strand region in the B-Strand primer is complementary or in any other way corresponds to the partial A'-strand sequence of the B-Strand. In fact as each sequence is a partial sequence of the A-strand or a partial complementary sequence of the A-strand, the current claim language permits for the partial A-strand region in the B-Strand primer and the partial A'-strand sequence of the B-Strand to be mutually exclusive and non-complementary. It is unclear how a primer can elongate a strand for which the primer has no complement in that strand.

As claim 1 is indefinite, dependent claims 5-10, 16, 19 and 20 are also indefinite.

Applicant does not argue against the above rejections.

New Rejections Necessitated by Amendment

35 USC § 112 First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 5-10, 16, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Step 3 of claim 1 has been amended to newly recite preparing two "free" nucleic acids the first having a sequence for elongating the B strand and the second for elongating the A-strand. No support for this new recitation is found in the originally filed application.

While support is found for one free nucleic acid, the B-strand elongating primer dissolved or "free" in a reaction solution (see paragraph 0064), the other primer is immobilized. This rejection can be overcome by Applicant pointing with particularity to the line(s) and page(s) where support for the two "free" nucleic acids as claimed can be found in the originally filed application.

New Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 5-10, 16, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al. (US 2001/0036632 published 2001), Oroskar et al. (1996, newly cited), Kawashima et al. (US 2005/0100900 published 2005 and filed 2003 and newly cited), Hamill (WO 2002/081743 published 2002 as submitted on the IDS, newly cited in this action), and Schmidt et al. (US Patent No. 6,416,951 issued 2002).

Regarding claim 1, Yu et al. teach methods of detecting a nucleic acids (entire publication), comprising the steps of:

(1) preparing a single-stranded nucleic acid having plural partial and sequential base sequences to be detected (A-strand) and a single-stranded nucleic acid having a base sequence complementary to a base sequence of the A-strand (B-strand) (see any one of the single strands of Gene A, B, or C and multiple primers to each single strand in Figure 1 and noting the complements bind to these primers in step 1B);

(2) preparing nucleic acids as primers each having one of the plural base sequences to be detected, immobilizing the respective primers independently in separate regions on a substrate, and preparing a primer array in which the respective

base sequences to be detected are distributed in the primer-immobilized regions (see Figure 1 steps 1A and 1B and claim 1);

(3) preparing a nucleic acid having a sequence complementary to a partial and sequential base sequence within the region between a 3'-end of the A-strand and the base sequence to be detected which is located nearest the 3'-end as a primer for elongating the B-strand (see Figure 1 step 1B and claim 1);

(4) performing PCR reactions using the A-strand and B-strand as templates, and using the primers immobilized on the substrate, and the primer for elongating the B-strand (see Figure 1 step 1C, see section *5. PCR Reactions* beginning at paragraph 0093, and see claim 1);

(5) forming a hybridized product of a nucleic acid corresponding to the A-strand which has been elongated and amplified as a result of the PCR reactions and bound to the substrate and a nucleic acid corresponding to the B-strand which has been elongated and amplified and has not bound to the substrate (see successive steps 1C through 1E of Figure 1); and

6) detecting the base sequence to be detected by detecting the hybridized product in the respective primer-immobilized regions in the array (note the labels for detection in Figure 1 and see claim 1).

Regarding claim 1, Yu et al. teach at least two immobilized primers, dual immobilized primers, but do not specifically teach an [A-strand] primer having a [A-strand] sequence where the complement or part of the complement of the [A-strand]

sequence is part of a [B-strand] (this is the reasonable interpretation of claim 1 in light of the indefinite recitations in the claim, as given above).

Regarding claim 1, Yu et al. do not specifically teach amplifying complementary strands with "free" primers prior and attachment to the solid phase.

Regarding claim 5, Yu et al. teach washing after the PCR reaction (see paragraph 0063, especially the 3rd sentence).

Regarding claims 6 and 7, Yu et al. teach fluorescent CY3 or CY5 labeled primers for synthesis of the new strands (see paragraph 0066 and also see paragraph 0006 for labeled probes).

Regarding claims 9, Yu et al. teach fluorescence detection and teach detection with intercalators and/or minor groove binders (see paragraph 0083) which inherently interact with double stranded nucleic acid, but do not specifically teach fluorescent intercalators.

Regarding claim 16, Yu et al. teach quantitative detection (see paragraph 0007).

Regarding claim 1, Hamill teaches PCR reactions using dual primers, one immobilized [A-strand] primer complementary to a region of the target strand [A-Strand] and a solution based primer [B-strand containing a complementary region of the A-Strand] complementary to the 3' terminus region of the immobilized primer complementary having a 3' terminus region complementary to a solution based primer (see Figure 2 and see lines 6-15 on p. 22).

Regarding claim 1, Hamill does not specifically teach that [B-strand] primer is immobilized.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the PCR reactions using dual immobilized primers of Yu et al. by using the immobilized [A-strand] primer for one of the immobilized primers for PCR reactions as suggested by Hamill with a reasonable expectation of success. The motivation to do so is provided by Hamill who teaches that methods using the immobilized [A-strand] permit deduction of sample sequence information, specifically the deduction of whether a polynucleotide is present in the sample from a microbial infection, disease condition, or genetic disorder (see lines 12-15 on p. 22). Both Yu et al. and Hamill teach methods using immobilized primers for polynucleotide detection, and so it would have been further obvious to one of ordinary skill in the art to substitute the immobilized primer of Hamill for one of the dual immobilized primers of Yu et al. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Regarding claim 1, Oroskar et al. specifically teach amplifying complementary strands with "free" primers in the liquid phase and attachment to the solid phase.

> "Simultaneously, the DNA strand complementary to the downstream and upstream primers is amplified in the liquid phase" (see 4th sentence of the 3rd paragraph on p. 1550 and see Figure 4).

Regarding claim 1, Kawashima et al. also specifically teach amplifying complementary strands with "free" primers in the liquid phase prior to attachment to the solid phase (see paragraph 0010)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the PCR reactions using dual immobilized primers of Yu et al. and Hamill by amplifying complementary strands with "free" primers in the liquid phase prior and attachment to the solid phase as suggested by Oroskar et al. and Kawashima et al. with a reasonable expectation of success. The motivation to do so is provided by Kawashima et al. who teach: " . . . it has been proposed to use one primer grafted to a surface in conjunction with free primers in solution in order to simultaneously amplify and graft a PCR product onto the surface" (see paragraph 0010 and referencing Oroskar, A. A., S. E. Rasmussen, H. N. Rasmussen, S. R. Rasmussen, B. M. Sullivan, and A. Johansson, *Detection of immobilised amplicons by ELISA-like techniques*, Clinical Chemistry 42:1547 (1996)). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Yu et al. and Hamill teach as noted above.

Regarding claims 8-10, Schmidt et al. teach fluorescently labeled probes hybridized to nucleic acids bound to arrays of distinct wells on a microplate and also teach fluorescent intercalators which bind to double stranded nucleic acids (see column

4 lines 1 to 8 and see *Intercalating Dyes* beginning at column 4 line 9) which can be detected with confocal microscopy (see column 4 line 50).

Regarding claims 19 and 20, Schmidt et al. teaches measurements in real time, that is intermittently (see column 3 lines 40-67), and where the nucleic acid detection are performed in the same well/container of a micro-plate (see column 4 lines 1 to 8).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Yu et al. and Hamill by using confocal microscopy to detect fluorescent intercalators on arrays as suggested by Schmidt et al. with a reasonable expectation of success. The motivation to do so is provided by Schmidt et al. who teach that their methods result in improved detection of functional antisense agents and can simultaneously measure the kinetics of complementary nucleic acid strand hybridizations (see column 1 lines 1-53). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
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